Nutrient-Exercise Timing: A Treatment Method for Type 2 Diabetes Mellitus and Obesity

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Introduction

Consistent exercise training is a method to treat and prevent type 2 DM and obesity due to increasing insulin sensitivity[1]. Insulin resistance is a crucial generator of metabolic disorders like type 2 DM[1]. Despite exercising to boost insulin sensitivity and lipid metabolism, each individual may respond differently to exercise. The type of nutrient intake and its timing throughout the day can alter metabolism during and after exercise[1]. A common nutritional approach is the intake of food high in glucose (e.g., carbohydrates and proteins) before, during, and after exercising to provide energy. An exercise session's timing corresponding with mealtime appears to be a factor in moderating the glycemic response to exercise, resulting in additional evidence for nutrient consumption timing being more vital than the daily amount of food ingested[2]. Physical activity promotes enhanced glycemic control through acute reactions and chronic transformations in local musculature[2]. These metabolic responses are mediated by the intensity, frequency, duration, and type of physical activity performed[2]. The workout schedule and nutrient intake are the most impactful when coordinating strategies to achieve the ideal results for insulin sensitivity and lipid metabolism in patients with type 2 DM and obesity.

Circadian clocks are known to direct functions throughout the body based on daily cycles. As a result, circadian rhythm plays a role in the process and schedule of metabolic pathways that manufacture glucose and secrete insulin[3]. An organism can be in one of two states: 1) active and seeking nourishment or 2) resting and fasting[4.] These two phases are

characterized by a molecular process that generates a rhythm of approximately 24 hours located in the suprachiasmatic nuclei (SCN) of the hypothalamus[4]. Glycemic stability is viewed as an example of the circadian control of the energy metabolism process[4]. Once peripheral organs receive information from the SCN, coordination of daily glucose uptake fluctuations, insulin release, and insulin sensitivity occur[5].

Circadian disruption increases the risk of developing type 2 demonstrating that circadian rhythm disruption can induce flawed glycemic control in healthy subjects[6]. Within these studies, insulin sensitivity and beta-cell responsiveness to glucose were diminished at dinner time in contrast to breakfast[6]. Additionally, there are indications that a diurnal rhythm of hepatic glucose production (HGP) contributes to morning (i.e., fasting) hyperglycemia in patients with type 2 DM[6]. The elevated HGP prior to breakfast could result from an extended nocturnal fast and possibly an outcome of circadian clock regulation of HGP supported by rodent studies[6]. Thus, nutrient-exercise timing becomes a potential therapeutic strategy to counteract the circadian disruption.

AMP-activated protein kinase (AMPK) is a heterotrimeric protein kinase that is one of the several metabolic sensors that transmits indicators reliant on energy to the mammalian clock[3]. Amplification of AMPK activity occurs in response to cellular ATP deficiency, especially in the liver during to extended fasting[3]. Additionally, glucose deprivation can cause the circadian period of SCN neurons to be altered, which can activate AMPK[3]. Further, AMPK and circadian clocks are known to affect regulatory elements of metabolism. The connection between AMPK and the circadian system indicates that treatment protocols that improve glycemic homeostasis by activating AMPK require a scheduled approach. Given these relationships, it's possible that timing exercise and nutrition intake could supplement the treatment

type 2 DM or facilitate prevention in patients with prediabetes.

Background

Roles of Glucose and Insulin

Insulin and Glucose work together to provide cells with the energy it needs via various metabolic pathways. Glucose is the most abundant monosaccharide in the human bloodstream. It is an important energy source for mammalian cells, and it is either consumed or synthesized by the body. The islets of Langerhans, also known as the pancreatic islets, are sections of the pancreas that house its endocrine cells. The beta cells of the pancreatic islets release a peptide hormone called insulin[7]. In a normal well-fed state, the digestion of carbohydrates leads to a rise in blood glucose which triggers an insulin response to control blood glucose concentration[8]. Insulin binds to a glycoprotein receptor on the cell membrane, assisting in managing normal glycemic levels by promoting cellular glucose uptake. Insulin is the primary hormone regulating the metabolism of carbohydrates, lipids, and proteins[7]. Insulin secretion occurs in two phases, the initial rapid phase, accompanied by a sustained period with reduced intensity.

Mechanism of Insulin Secretion, Glucose Uptake, and Lipid Metabolism

Elevated levels of glucose initiate the first step of insulin secretion[7]. High levels of glucose alert the pancreas to release insulin into the bloodstream. Glucose is a highly polar substance, which means the cell membrane's hydrophobic tails reject it; therefore, it enters cells by glucose transporter proteins (GLUT). Insulin facilitates diffusion of glucose in muscle tissue and adipose tissue by regulating the GLUT 4 glucose transporter[7]. Insulin stimulates lipid metabolism in

adipose tissue and muscle tissue[7]. When glucose and insulin levels decrease amidst the fasting period, the breakdown of lipid triglycerides in adipose tissue cells works to mobilize stored energy[7].

AMPK is a critical regulator of energy metabolism in muscle[9]. AMPK stimulates the usage of glucose and lipid stores along with the modification of macromolecules by autophagy[10]. In adipocytes and myocytes, AMPK regulates glucose's cellular utilization by impacting the Rab guanosine triphosphatase-activating proteins (GAPs) TBC1D1 and TBC1D4 (AS160)[11]. AS160 has a significant role in insulin-stimulated glucose intake to the adipocytes and myocytes[12]. TBC1D1 is an important AMPK substrate in muscle tissue, justifying AMPK as a crucial factor of activity-regulated glucose metabolism in muscle tissue[12]. AMPK stimulates glucose usage by phosphorylating targets involved in the trafficking of glucose transporters to increase glucose uptake into cells[10]. Additionally, AMPK phosphorylates hormone-sensitive lipase (HSL) and adipocyte triglyceride lipase (ATGL), which drives cells to use their lipid stores[10]. In obesity prevention and management, beta-oxidation of lipid stores is pivotal to prevent the build-up of free fatty acids that reduce insulin sensitivity.

Type 2 Diabetes Mellitus and the Connections to Obesity

There are two main types of diabetes mellitus; the less common type 1 diabetes mellitus is an autoimmune disease that causes the immune system to target the insulin-producing beta cells from the pancreas. There is a metabolic dysregulation in the more common type 2 DM involving impaired uptake and glucose utilization. In a healthy individual, blood glucose levels are regulated primarily by insulin, produced by the pancreatic beta-cells. Type 2 DM is characterized by hyperglycemia, insulin resistance, deterioration in insulin production, and pancreatic beta-cell

failure[13]. Various environmental, genetic, and behavioral factors can be attributed to the development of type 2 DM[13].

Type 2 diabetes mellitus can be caused, in part, by obesity which leads to impaired glucose tolerance and insulin resistance. When increased insulin concentrations are needed to sustain normal blood glucose levels (i.e., fasting – 70 – 99 mg/dL and postprandial - < 140 mg/dL), this indicates the development of insulin resistance[14]. In this case, beta-cells are no longer able to secrete enough insulin to combat the rise in blood glucose levels. The most meaningful pathophysiological event leading to type 2 diabetes mellitus is the insulin resistance of target tissues, including skeletal muscle and adipose tissue[14]. A preponderance of patients diagnosed with type 2 DM are overweight and have increased adipose tissue[13]. Greater body mass index (BMI), waist circumference, and waist-to-hip ratio are correlated with insulin resistance in patients[7]. The heightened quantity of free fatty acids cultivates insulin resistance at the cellular level and boosts hepatic VLDL (very low-density lipoprotein) production[7]. Therefore, calculated nutrient intake and exercise timing can significantly elevate insulin sensitivity and enhance lipid metabolism substantially when glucose levels are depleted.

Mechanisms of insulin resistance

Insulin resistance is acquired when a standard or elevated amount of insulin is produced and leads to insulin sensitivity impairment of glucose uptake at the cellular level[7]. Insulin resistance coupled with beta-cell failure and reduced insulin availability contributes to the hyperglycemia observed in type 2 DM[15]. Insulin resistance often manifests at post-receptor defects in insulin signaling, such as inadequate insulin receptor deficits and irregularities in GLUT 4 function[7]. Adipose tissue produces adipokines which modulate glucose homeostasis[7]. The most commonly discussed adipokines are Tumor Necrosis Factor (TNF)-alpha, leptin, adiponectin, and

resistin. TNF-alpha intensifies serine phosphorylation of IRS-1 and suppresses GLUT 4 expression, which contributes to insulin resistance[7]. In addition to obesity, a sedentary lifestyle is another crucial factor in the onset of insulin resistance and type 2 DM[16]. One of the adjustable factors of type 2 DM is a sedentary lifestyle; the importance of fitness training to improve insulin signaling and glucose metabolism is highly beneficial and cannot be overemphasized[16]. Increased lipid metabolism is imperative in obesity management and insulin resistance within the body. When patients exercise before a carbohydrate-rich meal, this assists in the beta-oxidation processes due to the bloodstream's lack of glucose. Insulin resistance is a leading cause of fatalities in western societies; however, nutritional changes associated with increased physical activity are the primary strategy for preventing insulin resistance[9].

The Role of Diet and Exercise on Diabetes Mellitus

Numerous variables can impact the risk of developing obesity and type 2 DM, ranging from societal to environmental influences that are eventually moderated by elevated energy consumption levels juxtaposed to energy expenditure[17]. Over several decades, patterns of nutrient consumption, often outside of a patient's control, are responsible for elevated calorie intake. The United States food supply is immense in fat and has been for many years. A nutrient inventory with tremendous amounts of sugar, fat, and energy density leads to a rise in voluntary energy intake resulting in weight gain[17]. A study with greater than 120,000 participants lacking chronic ailments and comorbidities demonstrated weight gain associated with intensified use of high-fat and sugar products, such as sugar-sweetened beverages and processed meats[17]. In comparison, subjects whose diet consisted of reduced sugar and fat such as fruits, vegetables, and whole grains observed results inversely related

to weight gain[17]. Positive dietary consumption changes are necessary, but incorporating exercise into the treatment of obesity and type 2 DM is vital.

It is well known that dietary regulation and physical activity are staples of type 2 DM management and avoidance[18]. Throughout a workout session, the repeated skeletal muscle contraction enhances glucose transport and insulin sensitivity in healthy subjects in one study[18]. In these healthy individuals, a brief fitness routine (7 days) elevated insulin-moderated glucose and GLUT 4 protein removal throughout the entire body[18]. In middle-aged insulin-resistant participants, limited physical activity (7 days) demonstrated increased insulin-moderated glycemic elimination throughout the body[18]. Literature documentation reinforces physical activity's function in improving the treatment outcomes in patients presenting with insulin sensitivity. Additionally, acute exercise intensifies GLUT 4 translocation to the sarcolemma membrane of striated muscle fiber cells[7]. Furthermore, lengthened physical activity raises GLUT 4 mRNA expression and enhances insulin sensitivity by heightening post-receptor insulin signaling[7].

Physical activity exerts significant modifications to glycemic quantities in patients diagnosed with type 2 DM. The Nurses' Health Study states that every two hours of diurnal standing or walking correlated to a 12% diminishment in the threat of being diagnosed with obesity and type 2 DM[17]. Additionally, one hour of brisk walking daily substantiated a 34% decrease in the risk of obesity and type 2 DM[17]. In a separate study, when training exceeded 150 minutes, HBA1c was reduced by 0.89%[19]. When exercising training was combined with dietary changes, HBA1c showed a reduction of 1.1%[19]. Physical activity assists in weight management, blood glucose regulation, and heightened oral glucose insulin sensitivity (OGIS). Medical care that enhances

insulin signaling and glucose uptake delivers significant clinical advantages in treating type 2 DM and obesity.

Significance of Nutrient-Exercise Timing on Type Two Diabetes Mellitus and Obesity

When patients incorporate a fitness routine weekly, it reduces the occurrence of type 2 DM and is vital in regulating blood glucose for patients with existing type 2 DM[2]. In some cases, the availability of fitness equipment is inadequate, or the ability to devote time to physical activity is not feasible. As a result, it is critical to determine what exercise and nutrient combinations have the most significant benefit in preventing metabolic disorders. Increasing evidence demonstrates that restricting carbohydrate consumption during physical activity can activate exercise training-induced conformations in myocytes to promote oxidative energy turnover and fatty acid (FA) transport[9]. The relationship between dietary consumption and training is essential to regulating intramyocellular lipid (IMCL) metabolism. Recent studies substantiate the significant inhibition of IMCL degradation in subjects consuming carbohydrates ahead of exercise and throughout the exercise session compared to participants who completed physical activity during a fasting period[9]. Additionally, energy output from FFA oxidation is stimulated by working out in the fasted state[9]. Exercise training is a strategic method to lower peak glucose to activate fat oxidation, which combats the increased levels of fat present for individuals suffering from type 2 DM and obesity.

Exercise training before carbohydrate consumption demonstrates beneficial effects in insulin sensitivity and lipid metabolism in subjects classified as obese[1]. During a 6-week research training program, lipid utilization enhancement was discovered and maintained before versus after carbohydrate ingestion[1]. OGIS elevation was documented in subjects who completed a workout before food consumption compared to

after food consumption. Exercise training prior to carbohydrate intake improved the remodeling of phospholipids and raised levels of energy awareness such as AMPK and GLUT 4 in exercising skeletal muscle[1]. This research study suggests that fitness training ahead of eating can enhance its adaptive reaction without elevating the workout's volume, intensity, or effort. Lipid metabolism is an essential mechanism with connections to training-induced alterations to crucial facets of metabolic wellness, such as the improvement of OGIS. Therefore, regulating the training responsiveness of lipid metabolism for individuals affected by type 2 DM and obesity requires nutrient exercise timing.

In a study concentrating on carbohydrate consumption, researchers scrutinized dinner as a time-related dietary response to obesity[20]. The research observations showed that subjects eating carbohydrates exclusively at dinner after 180 days had satiety (satisfied feeling of being full) scores that were 13.7% higher than baseline[20]. The experimental group demonstrated more significant decline in body mass index (BMI) and improved average body fat percentage compared with the control group[20]. These data demonstrate that the timing of nutrient intake, especially carbohydrates that are rich in energy, can be adjusted to help manage obesity. Consuming carbohydrates closer to bedtime, which for most individuals is the most extensive fasting period in the day, should assist in the breakdown of lipid stores throughout the day and the morning prior to exercising.

Insulin Sensitivity Restoration

A significant cause of insulin resistance is a high energy-dense diet[9]. Eating a high-fat diet (HFD) can swiftly damage glycemic tolerance and insulin sensitivity. Fitness training in the fasted phase noticeably drives energy usage through lipid metabolism. A 6-week study was conducted from these observations that investigated whether exercising in a fasted

phase is more potent than physical activity in the well-fed phase. The study aimed to recover data on glucose tolerance and insulin sensitivity throughout the body amidst an HFD[9]. In total, twenty-seven healthy volunteers received an HFD for six weeks, and ten of those volunteers carried out endurance exercise sessions over four days weekly in the fasted phase. Then researchers placed another ten subjects in a carbohydrate well-fed group (CHO), which consumed carbohydrates before and during the training session. The remaining seven volunteers were the control group who did not exercise. In the fasted state, body weight remained stable, and muscle GLUT 4 protein expression increased compared to the control group and CHO[9]. Only training in fasted state elevated AMPK phosphorylation and whole-body glucose tolerance[9].

On the contrary, CHO's physical activity was unsuccessful in providing a beneficial impact on glycemic homeostasis and insulin sensitivity[9]. This study demonstrates that a fitness routine in the fasted phase is more significant in altering muscle tissue and improving glycemic tolerance than well-fed phase physical activity. These treatment-induced conformations to myocytes could eventually be responsible for improvements in insulin sensitivity at the cellular level. Furthermore, AMPK demonstrates implications in exercise-related alterations in myocytes. Numerous studies have shown that even limited physical activity in the fasted phase enhances muscle AMPK activity in a superior manner compared to an equivalent fitness routine and considerable consumption of carbohydrates.[9] Amplification of GLUT 4 in skeletal muscle tissue can contribute to enhancements of OGIS ensuing physical activity before as opposed to after nutrient provision. Nutrient-exercise timing is imperative for reducing insulin resistance before the progression of obesity and type 2 DM.

Conclusion

The benefits of nutrient-exercise timing start with the improvements in lipid metabolism and insulin sensitivity. These two factors need significant enhancement in people suffering from type 2 DM and obesity. Physical activity and correctly timed nutrient consumption can have functional changes in insulin-signaling regulation. Exercise activates alternative molecular signals that address defects linked to insulin signaling in skeletal muscle, adipose tissue, the pancreas, and the liver. The repeated muscle contractions that occur throughout physical activities have shown improvement in glucose transport and insulin sensitivity in insulin-resistant patients. Future exercise training studies focusing on aspects of metabolic control should account for nutrient-exercise timing. Exercise and proper diet are critical for the management and prevention of type 2 DM and obesity. More strategic timing of training and appropriate nutrient intake is essential to prevent and combat type 2 DM and obesity.

Glossary & Abbreviations:

Adipocytes – a cell specialized for the storage of fat found in connective tissue.
Adipose Tissue – a specialized connective tissue consisting of lipid-rich cells called adipocytes.
AMPK - AMP-activated protein kinase
ATGL - Adipocyte triglyceride lipase
BMI - Body Mass Index**;** a weight-to-height ratio, calculated by dividing a patient's weight in kilograms by the square of the patient's height in meters and used as an indicator of obesity and underweight.
CHO - carbohydrate fed group
DM - Diabetes Mellitus

FA - fatty acid
Fasted state/phase/period – completely digested and absorbed last meal, and insulin levels are low or at baseline. General 3-4 hours after a meal.
Well-fed state/phase/period – occurs after a meal when the body is digesting the food and absorbing the nutrients (catabolism exceeds anabolism).
GLUT - Glucose Transporter Proteins
GLUT 4 - Glucose Transporter type 4; insulin-regulated, primarily in adipose tissues and striated muscle. Permits the facilitated diffusion of circulating glucose down its concentration gradient into muscle and fat cells. Plays a key role in regulating whole-body glucose homeostasis.
HFD - high-fat diet
HGP - Hepatic Glucose Production
HSL - Hormone-sensitive lipase
Hyperglycemia lab values – 180 – 200 mg/dL
IMCL - intramyocellular lipid
Muscle tissue – a specialized tissue found in animals that functions by contracting, thereby applying forces to different parts of the body. It consists of fibers of muscle cells connected in sheets and fibers.
Myocytes – type of cell found in some types of muscle tissue. Develop from myoblasts to form **muscles in a process known as myogenesis.**
Normal fasting blood glucose values – 70 – 99 mg/dL
Normal postprandial blood glucose lab values – 120 – 140 mg/dL
OGIS - Oral Glucose Insulin Sensitivity
Postprandial – occurring after a meal
RabGAP - Rab Guanosine Triphosphatases-activating proteins
RabGAP TBC1D4 (AS160) - Involved in insulin stimulation

RabGAP TBC1D1 - Regulates exercise-mediated glucose uptake into muscle. Implicated in obesity in humans and mice.
Satiety - the satisfying feeling of being full
SCN - Suprachiasmatic Nuclei
TNF - Tumor Necrosis Factor
Type 1 DM – Type 1 Diabetes Mellitus
Type 2 DM – Type 2 Diabetes Mellitus
VLDL - very-low-density lipoprotein; assembled in the liver from triglycerides, cholesterol, and apolipoproteins.
Waist circumference – a gauge of abdominal obesity, obtained by measuring the abdomen at the level of the superior iliac crest with a tape measure
Waist-to-hip ratio (WHR) – calculates the ratio of a patient's weight to their height, measures the ratio of the patient's waist circumference to their hip circumference to determine how much fat is stored patient's waist, hips, and buttocks.

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